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Schnabel, Renate B.; Pecen, Ladislav; Engler, Daniel; Lucerna, Markus; Sellal, Jean Marc; Ojeda, Francisco M.; De Caterina, Raffaele; Kirchhof, Paulus

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Atrial Fibrillation Patterns are associated with arrhythmia progression and clinical outcomes

Renate B. Schnabel[1,2], Ladislav Pecen[3], Daniel Engler[1,2], Markus Lucerna[4], Jean Marc Sellal[5], Francisco M. Ojeda[1,2], Raffaele De Caterina[6,7], Paulus Kirchhof[8,9]

1. University Heart Center Hamburg Eppendorf, Hamburg, Germany
2. German Center for Cardiovascular Research (DZHK) partner site Hamburg/Kiel/Lübeck (RBS, DE, FMO)
3. Medical Faculty Pilsen of Charles University, Czech Republic (LP)
4. Daiichi Sankyo Europe, Munich, Germany (ML)
5. Departement de Cardiologie, Centre Hospitalier Universitaire de Nancy, France
6. G. d'Annunzio University, Chieti, Italy
7. Fondazione G. Monasterio, Pisa, Italy (RDC)
8. Institute of Cardiovascular Sciences, University of Birmingham SWBH
9. UHB NHS Trust, Birmingham, UK (PK)

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Address for Correspondence:

Renate B. Schnabel, MD, MSc
University Heart Centre
Department of General and Interventional Cardiology
Martinistr. 52
20246 Hamburg, Germany
Phone: +49-1522-2816064
E-mail: r.schnabel@uke.de

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Abbreviations: AF, atrial fibrillation; CI, confidence interval; OR, odds ratio; PAF, paroxysmal AF; PREFER in AF, PREvention oF thromboembolic events - European Registry in Atrial Fibrillation; standard deviation, SD; TIA, transitory ischemic attack

Abstract [word count 250]

Objectives Determinants of atrial fibrillation (AF) patterns and of progression of earlier forms to permanent AF, and their relation with outcome are still poorly understood.

Methods We examined AF patterns (paroxysmal, persistent, permanent), rate and predictors of AF progression, and outcomes in the PREFER (PREvention oF thromboembolic events-European Registry) in AF. The primary analysis was performed in the PREFER in AF prolongation data set (N=3223 AF patients with complete 1-year follow-up, mean age 72±9 years, 40% women). Sensitivity analyses were performed using the PREFER in AF study (N=6390 patients).

Results AF progressed to more persistent types in 506 patients (17%). Permanent AF was associated with development of heart failure at one year (odds ratio (OR) 1.80, 95% confidence interval (CI) 1.06-3.07, P=0.03) compared to paroxysmal AF (PAF), which was confirmed in the entire cohort. In multivariable-adjusted models, sinus rhythm at baseline, AF duration, cardioversion, hyperthyroidism, valvular heart disease, diabetes mellitus, and heart failure were predictors of AF progression (area under the receiver operating characteristic curve 0.60, 95% CI 0.57-0.63). Results were similar when we restricted analyses to patients with AF duration <1 year. AF progression showed an association with coronary events over one year (OR 2.27, 95% CI 1.22-4.19, P=0.0074).

Conclusions Permanent AF at baseline was associated with incident heart failure. A substantial proportion of well-managed AF patients showed AF progression over one year. AF progression itself was not strongly related to outcome and may indicate the need to refine the current classification of AF types to enhance clinical utility.

What is already known about this subject?

Atrial fibrillation appears to be a progressive disease. Non-paroxysmal atrial fibrillation has been associated with adverse outcomes. Clinical predictors of atrial fibrillation may exist.

What does this study add?

This study shows that almost half of the patients with atrial fibrillation duration less than one year were in permanent atrial fibrillation. Atrial fibrillation revealed a significant progression rate over one year (17%). Permanent atrial fibrillation was associated with increased risk of developing heart failure. Determinants of atrial fibrillation progression comprised atrial fibrillation duration, diabetes mellitus, heart failure, hyperthyroidism, sinus rhythm at baseline, cardioversion, and valvular heart disease.

How might this impact on clinical practice?

Atrial fibrillation is a progressive disease during a comparatively short one-year time frame which needs to be considered when treating patients with the rhythm disorder. Modifiable clinical predictors of atrial fibrillation progression exist and may represent targets for intervention to reduce progression rate. New, prognostically relevant patterns of atrial fibrillation may need to be defined.

INTRODUCTION

Atrial fibrillation (AF) burden is increasing worldwide,[1] and constitutes a progressive disease in most cases.[2, 3] The arrhythmia carries a high risk of complications such as thromboembolic events, heart failure, and coronary events. Anticoagulation therapy used to reduce stroke risk increases bleeding disposition. Chronic AF patterns (persistent, long-standing persistent, and permanent AF) appear to be associated with an increased thromboembolic risk compared to PAF as shown by a recent meta-analysis.[4] Early AF recurrence and persistent AF have been associated with a higher mortality and an increased risk of stroke and heart failure in the community compared to paroxysmal types or lack of recurrence after an initial episode.[5] In patients, disease progression seems to be accompanied by a higher risk of adverse events.[6, 7] Furthermore, mortality is increased with longer episodes of AF, which may be confounded by clinical characteristics in patients with non-PAF.[8, 9] Current guidelines categorize AF into paroxysmal, persistent, long-standing persistent and permanent based on duration and termination of episodes. In addition, new onset disease represents a specific category. The relevance of AF patterns in clinical practice has not been fully defined. Further, the progression rate of AF and its clinical correlates remain unclear. A prior publication addressed predictors for AF progression in patients with PAF.[10] Hypertension, age, transient ischemic attack (TIA) or stroke, chronic obstructive pulmonary disease and heart failure (HATCH score) were identified as predictors of AF progression in PAF. The score replicated only modestly in independent cohorts.[8, 11] Therefore, a systematic examination of indicators of AF progression across the spectrum of AF types is required. Further data are needed relating AF type to cardiovascular outcomes in clinical practice. Therefore, we used the PREFER in AF (PREvention oF thromboembolic events - European Registry in Atrial Fibrillation) registries to examine the clinical impact of AF type and progression on prognosis and to elucidate predictors of disease progression.

METHODS

Study sample

We analyzed two similarly structured contemporary European registries on epidemiology, management and outcome in all-comers with AF, the PREFER in AF and its Prolongation study. The study design and primary results of PREFER in AF have been published previously.[12]

In brief, the PREFER in AF registry enrolled 7,243 AF patients at least 18 years across seven European countries from 2012-2014. At one year, information was collected by questionnaire with last follow-up in January 2014. Enrolment took place at 461 sites, which were predominantly cardiology practices and hospitals. N=6412 patients completed follow-up. From N=22 patients AF type at baseline was missing, leaving N=6390 patients for analysis.

The PREFER in AF Prolongation registry is an extension of the PREFER in AF registry that enrolled N=3597 patients from June 2014 to May 2015 and including sites that had already participated in the PREFER in AF registry (N=412). They had to be on non-vitamin K antagonist oral anticoagulant treatment at enrolment. As data on AF type were available at baseline and follow-up in the PREFER in AF Prolongation registry, the primary analysis was performed in this cohort. N=3223 had complete 1-year follow-up information, last follow-up June 2016. A total of 3223 patients had complete 1-year follow-up data at the last follow-up (June 2016). As data on AF type at baseline were missing in 13 patients, the analysis was performed in 3210 patients. The PREFER in AF data set was used for validation using available information on baseline AF type.

Clinical variables

All patients had AF documented by ECG and diagnosed by a physician. AF pattern information was in accordance with the ESC/EACTS guidelines.[13] As there was a small number of

patients with longstanding persistent AF (N=132 in PREFER in AF Prolongation; N=516 in PREFER in AF) this category was combined with permanent AF for analysis. A total of 55 patients in the PREFER in AF Prolongation and 103 in the PREFER in AF study were classified as permanent AF but showed sinus rhythm on study ECG, and were categorized as persistent AF. Sensitivity analyses confirmed that the results did not change markedly after reclassification of these individuals. We performed additional analyses in patients with AF onset <12 months.

Outcomes

AF type at 1-year follow-up was the primary outcome. We assumed a disease progression if patients with PAF at baseline were classified as persistent or permanent AF at follow-up and if patients with persistent AF on enrolment were diagnosed with permanent AF after one year. Prevalent cardiovascular disease incorporated coronary heart disease, peripheral arterial disease and myocardial infarction.

We evaluated the following disease outcomes: ischemic stroke/ (TIA) /arterial embolism, coronary events (acute coronary syndrome/coronary revascularization), heart failure (physician diagnosis and/or reduced left ventricular ejection fraction), and major bleeding (cerebrovascular bleeding, major gastrointestinal or other bleeding events requiring hospitalization or blood transfusion). AF type and outcomes were assessed at follow-up.

Local Ethics Committees in Austria, Germany, Switzerland, Italy, Spain, France and UK provided their approval as required by national regulations. All participants provided written, informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Statistical analyses

Data were analyzed separately for the PREFER in AF Prolongation and PREFER in AF studies. Complete case analysis was performed, after we had formally tested whether data were missing

completely at random. Data are presented as mean±standard deviation (SD) for continuous variables, or median (25th/75th percentile) for skewed variables, and as number (percentage) for discrete variables. We compared the overall proportion of individuals with progression to patients stable or less advanced disease state by McNemar's test. We performed logistic regression analyses to relate baseline variables to progression of AF over one year in PREFER in AF Prolongation. A logistic stepwise variable selection model as implemented in SAS was applied to identify the strongest predictors of AF progression. All baseline variables were permitted to enter the model. The C-statistic as implemented in SAS proc logistic using ROC statement (the area under the Receiver Operating Characteristic (ROC) curve (AUC)) was calculated to understand the discriminatory ability of the combination of all selected clinical baseline variables to predict AF progression. We compared the discriminatory ability of our model to the previously reported HATCH score using its variables hypertension, age, transient ischemic attack (TIA) or stroke, chronic obstructive pulmonary disease and heart failure.[6]

AF progression at follow-up was related to outcomes using logistic regression analyses. Furthermore, unadjusted and multivariable-adjusted regression analyses were performed to relate baseline AF type to one-year outcomes, adjusted for age, sex, and country. Comparison of persistent and permanent AF to PAF was used as the reference. Patients with prevalent heart failure at baseline were excluded from analyses on the incident condition.

We performed sensitivity analyses for regression analyses using PAF vs. non-PAF types combined. For these analyses, sinus rhythm was not permitted to enter the stepwise model. Results are based on PREFER in AF Prolongation data if not stated otherwise.

SAS software version 9.4 (Cary, North Carolina, USA) was used for statistical computations. A two-tailed significance threshold of 0.05 indicated statistical significance.

RESULTS

Baseline patient characteristics

In **Table 1** baseline characteristics of the PREFER in AF Prolongation patients are detailed by type of AF. Patients with permanent AF were older, had a longer AF duration, and accumulated cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, chronic pulmonary disease, and valvular heart disease. Individuals with permanent AF also had the highest proportion of a history of thromboembolic events and major bleedings. Almost half of the patients with persistent AF had a cardioversion in the year prior to enrolment ($p<0.05$ compared to other AF patterns). Clinical characteristics were similar in the PREFER in AF registry (**Supplementary Table 1**). The distribution of AF type at baseline for the total PREFER in AF Prolongation study and for the subgroup of patients with AF duration <1 year, N=1738 are shown in **Supplementary Figure 1**. Among patients with AF duration <1 year, approximately half (N=555, 52%) had non-paroxysmal types of AF at baseline.

Table 1. Baseline characteristics of PREFER in AF Prolongation patients by atrial fibrillation type

Variables	Paroxysmal N=1337	Persistent N=814	Permanent N=1059	P Value
Age, years (SD)	70.9±9.4	70.4±9.5	75.4±8.5	<0.001
Women, N (%)	595 (44.5)	291 (35.7)	399 (37.7)	<0.001
Body mass index, kg/m² (SD)	27.7±4.9	28.2±5.1	28.5±4.8	<0.001
Systolic blood pressure, mm Hg (SD)	135±16	134±17	133±16	0.09
Heart rate, bpm (SD)	71.8±18.3	76.6±19.2	76.4±14.8	<0.001
Atrial fibrillation duration, years	1.2 (0.2, 4.0)	0.8 (0.2, 2.8)	2.7(1.0, 7.3)	<0.001
Arterial hypertension, N (%)	1011 (75.8)	601 (74.3)	845 (79.8)	0.01

Table 1. Baseline characteristics of PREFER in AF Prolongation patients by atrial fibrillation type

Variables	Paroxysmal N=1337	Persistent N=814	Permanent N=1059	P Value
Ever smoking, N (%)	461 (35.6)	288 (36.1)	363 (35.0)	0.9
Alcohol abuse, N (%)	40 (3.0)	36 (4.5)	42 (4.0)	0.2
Diabetes mellitus, N (%)	305 (22.9)	182 (22.4)	256 (24.2)	0.63
Dyslipidaemia, N (%)	546 (41.6)	303 (37.9)	458 (43.9)	0.04
Prevalent cardiovascular disease, N (%)	286 (21.5)	149 (18.8)	257 (24.5)	0.01
Prevalent heart failure, N (%)	278 (20.8)	227 (28.0)	292 (27.6)	<0.001
History of ischemic stroke/TIA/other ischemic-thromboembolic event, N (%)	226 (16.9)	103 (12.7)	198 (18.7)	<0.001
Chronic renal insufficiency, N (%)	229 (17.4)	150 (18.6)	251 (23.9)	<0.001
Chronic hepatic disease, N (%)	10 (0.8)	7 (0.9)	14 (1.3)	0.34
Hyperthyroidism, N (%)	60 (4.5)	37 (4.6)	29 (2.8)	0.05
Chronic obstructive pulmonary disease, N (%)	105 (7.9)	62 (7.6)	111 (10.5)	0.03
Major gastrointestinal/cerebrovascular/ other bleeding events, N (%)	39 (2.9)	17 (2.1)	65 (6.1)	<0.001
Sinus rhythm, N (%)	968 (72.8)	362 (44.6)	0 (0.0)	<0.001
Heart valve dysfunction, N (%)	425 (32.0)	314 (38.8)	450 (42.9)	<0.001
Antiarrhythmic drugs, N (%)	856 (64.0)	498 (61.2)	426 (40.2)	<0.001
Cardioversion in the last 12 months, N (%)	350 (26.2)	388 (47.7)	122 (11.5)	<0.001

Mean ± standard deviation (SD) or median (25th/75th percentile) for skewed data are provided for continuous variables, number and percent for discrete values. Prevalent cardiovascular disease indicated coronary heart disease, peripheral arterial disease and myocardial infarction. TIA stands for transient ischemic attack.

AF progression at one-year follow-up was observed in N=506 (16.5%) of patients. **Figure 1A** shows that N=242 (19%) of individuals with PAF and N=264 (34.4%) with persistent AF had a progression. In patients with a new diagnosis of AF <1 year, the progression rate was N=217 (20.4%) (**Figure 1B**). Whereas the majority of PAF patients remained in PAF, similar proportions of patients with persistent AF remained in the same category or showed progression over one year. Among patients who transitioned into permanent atrial fibrillation after one year, 12.8% were on antiarrhythmic drug therapy, 15.4% had undergone cardioversion and 8.3% had had an ablation therapy.

A regression of AF type was observed in persistent AF patients (N=115, 32%).

Type of AF and outcomes

In unadjusted logistic regression analyses we identified statistically significant associations of AF type with incident heart failure (OR 1.80, 95% CI 1.06-3.07; P=0.029), which lost statistical significance after multivariable adjustment (**Table 2**). In the larger PREFER in AF registry there was an association of similar magnitude for both, permanent and persistent AF versus PAF (**Supplementary Table 2**). Further, permanent AF compared to PAF was inversely related to coronary events, but no signal was seen in PREFER in AF.

Table 2. Logistic regression analyses for atrial fibrillation type in relation to one-year outcomes in PREFER in AF Prolongation

Outcome	**OR**	**95% CI**		**P value**
Stroke/TIA/arterial embolism, N=49				
Persistent vs. PAF	1.46	0.72	2.94	0.29
	1.12	0.54	2.32	0.77

Table 2. Logistic regression analyses for atrial fibrillation type in relation to one-year outcomes in PREFER in AF Prolongation

Outcome	OR	95% CI		P value
Permanent vs. PAF	1.28	0.65	2.51	0.48
	1.06	0.52	2.15	0.87
Heart failure*, N=75				
Persistent vs. PAF	1.30	0.70	2.41	0.40
	1.48	0.77	2.86	0.24
Permanent vs. PAF	1.80	1.06	3.07	0.03
	1.52	0.86	2.71	0.15
Coronary event, N=50				
Persistent vs. PAF	1.05	0.56	1.98	0.87
	0.89	0.45	1.75	0.72
Permanent vs. PAF	0.45	0.21	0.98	0.04
	0.41	0.18	0.90	0.03
Major bleeding, N=62				
Persistent vs. PAF	1.39	0.71	2.72	0.34
	1.26	0.63	2.53	0.51
Permanent vs. PAF	1.83	1.01	3.31	0.05
	1.52	0.81	2.83	0.19

*Patients with heart failure at baseline were excluded from analyses (N=797).
The upper row model is unadjusted. The lower row model is age-, sex- and country-adjusted.

Predictors of AF progression

Table 3 shows results of the regression analyses relating clinical variables to AF progression. AF duration (OR 0.95, 95% CI 0.93-0.98; P<0.001) and sinus rhythm at baseline (OR 0.63, 95% CI 0.51-0.77; P<0.0001) were inversely related to AF progression in unadjusted analyses. Prevalent heart failure (OR 1.38, 95% CI 1.12-1.71; P<0.001), hyperthyroidism (OR 1.68, 95% CI 1.09-2.59; P=0.02) valvular heart disease (OR 1.37, 95% CI 1.13-1.66; P<0.001), and cardioversion (OR 1.32, 95% CI 1.08-1.63; P=0.01) showed a positive association with

progression. These variables and diabetes mellitus were selected as the strongest predictors of AF progression by logistic stepwise selection using all variables presented in **Table 3** (**Figure 2**). The C-statistic of the selected variables combined was 0.64 and significantly differed from the results when using the HATCH score, C-statistic 0.52, P=0.0001. Results from stepwise selection models in patients with AF progression <1 year are shown in **Supplementary Figure 2**. The selected variables were comparable with the total cohort except for hyperthyroidism, heart valve dysfunction and diabetes that did not enter the model. In addition, prevalent cardiovascular disease with a positive association and antiarrhythmic drug use with an inverse association were selected. Results of regression analyses for paroxysmal versus non-paroxysmal AF are shown in **Supplementary Table 3**. The stepwise regression model excluding sinus rhythm as a predictor variable is provided in **Supplementary Table 4.**

Table 3. Logistic regression analysis for predictors of progression of atrial fibrillation over one year in PREFER in AF Prolongation

Variable	**Odds ratio**	**95% Confidence interval**		**P value**
Age	1.01	1.00	1.02	0.30
	1.00	0.99	1.02	0.35
Body mass index	1.00	0.98	1.02	0.82
	1.00	0.98	1.02	0.70
Systolic blood pressure	1.00	0.99	1.03	0.41
	1.00	0.99	1.01	0.76
Heart rate	1.01	1.00	1.02	<0.001
	1.01	1.00	1.02	0.02
Atrial fibrillation duration	0.95	0.93	0.98	<0.001
	0.95	0.93	0.98	<0.001
Arterial hypertension	0.92	0.73	1.15	0.45
	0.88	0.70	1.11	0.30
Ever smoking	1.00	0.81	1.22	0.96
	0.99	0.80	1.23	0.91
Alcohol abuse	0.66	0.37	1.18	0.16

Table 3. Logistic regression analysis for predictors of progression of atrial fibrillation over one year in PREFER in AF Prolongation

Variable	Odds ratio	95% Confidence interval		P value
	0.68	0.38	1.24	0.21
Diabetes mellitus	1.22	0.98	1.52	0.07
	1.23	0.98	1.53	0.07
Dyslipidaemia	0.95	0.78	1.15	0.58
	0.94	0.77	1.15	0.57
Prevalent cardiovascular disease	1.11	0.88	1.39	0.39
	1.12	0.88	1.42	0.35
Prevalent heart failure	1.38	1.12	1.71	<0.001
	1.37	1.10	1.71	<0.001
Stroke/ TIA/ thromboembolism	1.05	0.81	1.36	0.71
	1.01	0.78	1.32	0.92
Chronic renal insufficiency	0.94	0.74	1.20	0.64
	0.96	0.75	1.23	0.74
Chronic hepatic disease	2.14	0.93	4.92	0.07
	2.00	0.87	4.64	0.10
Hyperthyroidism	1.68	1.09	2.59	0.02
	1.76	1.14	2.72	0.01
Chronic obstructive pulmonary disease	1.01	0.72	1.43	0.94
	0.95	0.67	1.34	0.75
Major bleeding	0.68	0.38	1.23	0.20
	0.63	0.35	1.14	0.12
Heart valve dysfunction	1.37	1.13	1.67	<0.001
	1.38	1.12	1.69	<0.001
Sinus rhythm	0.63	0.51	0.77	<0.001
	0.65	0.53	0.80	<0.001
Antiarrhythmic drugs	0.99	0.82	1.20	0.91
	1.03	0.85	1.26	0.75
Cardioversion in the last 12 months	1.32	1.08	1.63	0.01
	1.36	1.10	1.69	<0.001

ORs are per one unit increase for continuous variables or for the condition present for

Table 3. Logistic regression analysis for predictors of progression of atrial fibrillation over one year in PREFER in AF Prolongation

Variable	Odds ratio	95% Confidence interval	P value

dichotomous variables. The upper row model is unadjusted. The lower row model is age-, sex- and country-adjusted. Data are based on N=3063 individuals with complete follow-up information.

In **Table 4** AF progression in relation to outcomes is shown. We observed an association of AF progression with coronary events (OR 2.27, 95% CI 1.22-4.19; P=0.01).

Table 4. Univariate logistic regressions for atrial fibrillation progression in relation to one-year outcomes in PREFER in AF Prolongation

Outcome	Odds ratio	95% Confidence interval		P value
Stroke/TIA/arterial embolism, N=47	0.47	0.17	1.30	0.14
Heart failure, N=70*	1.26	0.68	2.33	0.45
Coronary event, N=49	2.27	1.22	4.19	0.01
Major bleeding, N=59	0.57	0.24	1.33	0.18

Hazard ratios and 95% CIs are provided. Data are based on N=3063 individuals with complete follow-up information. *Patients with heart failure at baseline were excluded from analyses (N=797).

The sensitivity analyses for PAF versus non-PAF types showed similar results with the same directions of associations (**Supplementary Table 5**). The strength of association was weaker due to the small number of patients with PAF progression to more permanent types (N=242). AF duration in PAF was not associated with progression.

DISCUSSION

Main findings

In our AF cohort the majority of patients was in non-PAF. Even in individuals with an AF duration of <1 year almost 50% had persistent or permanent AF. The progression rate over one year was substantial. Permanent AF was associated with new development of heart failure, and AF was associated with coronary events. We identified clinical parameters that were associated with AF progression, but there is a clear need to identify better markers for AF progression.

AF type and progression

It is recognized that clinical characteristics of patients differ across AF type. Patients with permanent AF are older and show more, possibly AF-related, complications such as a history of thromboembolic events, heart failure or bleeding besides the longer AF duration.

The majority of patients presenting in clinical practice are in non-PAF. We further saw that when first diagnosed, AF did not necessarily evolve from PAF. Among patients with a diagnosis of AF within 12 months, 47% were classified as non-PAF. In both groups, patients with a long-standing diagnosis of AF and with AF duration <1 year, we observed a substantial progression. In the latter, one fifth of the patients developed chronic forms of AF in one year. A higher proportion of individuals in persistent AF progressed compared to PAF patients.

We also observed a regression in AF type from persistent to PAF. Some patients may be defined as persistent while presenting with similar AF burden and duration as others who are defined as paroxysmal.[11] AF regression is probably a biological fact and has been reported earlier.[12] The relatively large proportion of patients that was classified as persistent AF at baseline and PAF after one year, however, may be due to cardioversion therapy prior to baseline that automatically classifies patients into persistent AF whereas later on, paroxysms of AF that terminate spontaneously may occur.

Predictors AF progression

In multivariable models, we identified several clinical predictors of AF progression. Among these, heart failure has been related to AF incidence and progression.[6, 13] It is pathophysiologically plausible that structural and functional cardiac changes contribute to the initiation and perpetuation of AF. Heart failure has been reported as an indicator of AF progression in the Euro Heart Survey.[14] In this cohort the HATCH score was developed in PAF patients.[15] In the present study, we extend this finding towards a cohort across the spectrum of PAF and persistent AF and identified the following additional predictors: the duration of AF, diabetes, hyperthyroidism, and valvular disease. In our cohort, the HATCH score replicated poorly as has been reported in other studies.[2, 8] These findings underlines that with current variables it is difficult to predict AF progression.

Of note, the time since AF diagnosis was inversely related to progression, indicating a faster dynamic in change early after the first diagnosis of AF, with a possible stabilization of disease phenotype later during the disease course. A higher progression rate early during PAF has been reported in the Canadian Registry of Atrial Fibrillation, but with a much lower percentage, i.e. 8.6%.[14] The absolute rate of AF progression will depend on patient characteristics as well as on the intensity of rhythm control treatment.

Diabetes and hyperthyroidism as well as valvular heart disease constitute treatable conditions. It seems sensible to consider good management of these conditions to slow AF progression, especially in patients undergoing rhythm control therapy. Hyperthyroidism is well known in association with AF incidence and recurrence.[15, 16] We can now demonstrate that it is also correlated with progression of AF type. There are two likely explanations: Mechanisms triggered by hormonal imbalance that lead to AF onset also produce the substrate for AF recurrence and perpetuation of disease.[17] Furthermore, hyperthyroidism limits anti-arrhythmic drug therapy, in particular with amiodarone, and may result in a higher AF progression rate. We could not

confirm hypertension, TIA or stroke nor chronic obstructive pulmonary disease as strong predictors of AF progression as reported in the HATCH score. The lack of validation may be due to underlying differences in the studies. In particular, our cohort comprised a broader range of AF types and may thus not be comparable directly.

A possible correlation of progression of PAF with mortality has been reported.[3, 6] We could demonstrate an association with coronary events, but not with other AF-related events, which may be limited by the comparatively small number of outcomes during the one year observational period.

AF type and outcome

Over the one year follow-up period we observed an association for AF type with coronary events and a borderline association with heart failure incidence. For coronary events the direction of association was inverse and only present for permanent AF compared to PAF. No significant results for persistent versus PAF were demonstrated. In addition, there was no signal of an association in PREFER in AF with more than three times the number of outcomes. Therefore we assume that the results are spurious findings.

Similarly as discussed for AF progression, heart failure and AF are two closely interrelated diseases that share common pathophysiological pathways and perpetuate each other.[18] Hence, permanent AF may reflect a more advanced AF disease state that could be associated with manifestation of heart failure. The presence of AF could additionally worsen ventricular function as has been shown for patients with tachycardiomyopathy.[19, 20] Our associations seen over one year were consistent in both registries; however, validation in independent cohorts is required. Ongoing clinical trials evaluating heart failure as an outcome will examine the impact of maintaining sinus rhythm on ventricular function.[21]

We could not demonstrate an impact of AF pattern on thromboembolic events, but the low overall event rate observed in the PREFER registries precludes firm conclusions. A trend

towards higher risk of thromboembolic events in chronic AF compared to PAF was confirmed by a meta-analysis comprising almost 100,000 patients.[4] There was substantial heterogeneity among studies and in the individual studies, the association was not uniform. For example, in large, contemporary trials such as the ROCKET-AF study patients with persistent AF had higher thromboembolic event rates,[22] whereas in the Euro Heart Survey there was no clear difference in event rates between PAF and persistent AF.[23] In the present study, the majority of patients received oral anticoagulation therapy and showed a low thromboembolic event rate across AF subtypes accordingly. Beyond the comparison of PAF versus more persistent types, we further had the opportunity to examine the subgroups of permanent and persistent AF in relation to outcomes. However, we could not demonstrate a gradient in associations for thromboembolic events either. In line with the recent meta-analysis [4] we could not show an association of AF type with bleeding risk.

Limitations

The number of events over the one-year follow-up period was relatively small. However, we had good power to detect moderate to strong associations.[6] A high follow-up rate of 95% should largely eliminate bias due to incomplete information on outcomes. Inherent to the currently used AF patterns, which do not reflect the true AF burden, we might have seen different associations if the actual frequency and duration of AF episodes had been known. Interactions in the relations of the different predictors of AF progression are pathophysiologically plausible. A formal statistical testing was not performed due to the comparatively small number of cases.

Further, it needs to be considered that the current definition of AF subtypes incorporates both, pathophysiological and physician's subjective assessment where psychosocial factors and management strategies may play a role. In older and sicker patients including those with heart failure AF will more likely be accepted as permanent by the treating physician and fewer attempts at restoration of sinus rhythm will be made. The AF subtype definition therefore not

necessarily reflects the pathophysiology of the disease course but many factors in the patient physician interaction. Therefore, the classification is not objective and may be subject to bias.

The strength of our study is that we present data in a large, contemporary cohort that provides insights into AF distribution and its progression and a broad spectrum of clinically relevant outcomes using the guideline-recommended classification system.

Conclusion

In summary, AF is a progressive disease in most patients with a significant annual progression rate identified in two AF all-comer cohorts. Clinical predictors of progression have also been identified. Future studies need to demonstrate whether the progression rate can be reduced by targeting modifiable predictors. More importantly, it needs to be shown whether AF progression is associated with adverse events, and whether prevention of progression improves outcomes in AF and needs to be integrated into AF management.

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COMPETING INTERESTS

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FIGURE LEGENDS

Figure 1. The number and proportion of atrial fibrillation types at baseline and at one year follow-up are provided in A) the total PRFER in AF Prolongation study (N=3063) and B) patients with atrial fibrillation diagnosed <1 year (N=1063). Slightly lower numbers compared to the baseline table are due to missing information of atrial fibrillation type at follow-up.

Figure 2. Logistic stepwise selection model for predictors of atrial fibrillation progression in the PREFER in AF Prolongation study. Odds ratios and 95% confidence intervals are provided per standard deviation (duration of atrial fibrillation) or presence of the condition. The continuous variable atrial fibrillation duration entered analyses logarithmically transformed log(1+atrial fibrillation duration in years). Cardioversion indicates cardioversion in the last 12 months. Analyses were performed in the subgroup of patients with all variables available (N=2495).